



REVIEW ARTICLE

Imaging of Renal Angiomyolipomatosis

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Abstract

Angiomyolipoma is a type of benign renal tumor. It is sporadic and isolated in 80% of cases. The remaining 20% is associated with tuberous sclerosis complex or pulmonary lymphangioleiomyomatosis. Generally, angiomyolipomas manifest themselves as angiomyolipomatosis, in which the angiomyolipomas are larger, bilateral, and widespread. Understanding whether angiomyolipomas are present in the context of angiomyolipomatosis is of considerable importance because it might be associated with malignant lesions. This article provides an overview of the radiological features of renal angiomyolipomatosis under different imaging techniques such as ultrasound, computed tomography, and magnetic resonance.

Keywords: angiomyolipoma; lymphangioleiomyomatosis; PEComa; renal angiomyolipomatosis; tuberous sclerosis

Received: 05 September 2018; *Accepted after revision:* 21 October 2018; *Published:* 14 November 2018

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How to cite: Greco F, Mallio CA, Cirimele V, D'Alessio P, Beomonte Zobel B, Grasso RF. Imaging of renal angiomyolipomatosis. *J Ren Hepat Disord.* 2018;2(2):10–19.

Doi: <http://dx.doi.org/10.15586/jrenhep.2018.37>

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Introduction

Angiomyolipoma (AML) is a type of benign renal tumor, with an estimated prevalence of 0.3–3% of all renal tumors and a greater female predilection (1, 2). It is characteristically a solid “triphasic” tumor composed of dysmorphic blood vessels, smooth muscle components, and mature adipose tissue which may be present in varying amounts (3). AML was once considered a hamartoma and, most recently, a choristoma; it is now considered a part of perivascular epithelioid cell tumors (PEComa) (4–6). PEComa are mesenchymal neoplasms formed by nests and sheets of epithelioid and spindle cells that show immunoreactivity for both smooth muscle and melanocytic markers (7). The PEComas now include AML, pulmonary clear cell “sugar” tumor and lymphangioleiomyomatosis (LAM),

primary extrapulmonary sugar tumor, clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres, abdominopelvic sarcoma of perivascular epithelioid cells, and other neoplasms with similar characteristics (8). Renal angiomyolipomatosis is a common manifestation in patients with tuberous sclerosis (TS) and LAM, where AMLs are larger, multiple, almost always bilateral, and have a greater predisposition to bleeding. AML is sporadic and isolated in 80% of cases, while the remaining 20% is associated with tuberous sclerosis complex (TSC) or pulmonary LAM (9, 10). Radiologically, the sporadic AML is predominantly classified into classic (common) and fat-poor AML (uncommon). Fat-poor AML is further classified into three subtypes: hyperattenuating AML (approximately 4.5% of all AMLs), isoattenuating AML (rare), and AML with epithelial cyst

(rare). Another type of sporadic AML is epithelioid AML (rare). Syndromic AML is subdivided into AML in TSC and AML in LAM (11). The majority (>80%) of AMLs are detected incidentally during imaging. Most patients are asymptomatic when AML is diagnosed (10). The most common presentation is spontaneous retroperitoneal hemorrhage, although this happens in less than 15% of cases (10). Other clinical presentations are anemia, hematuria, palpable mass, flank pain, urinary tract infection, or renal failure (12, 13). As most classic AMLs do not increase in size and remain asymptomatic, the management is conservative. However, some grow gradually, showing a growth rate of 5% or 0.19 cm per year (14, 15). Oesterling et al. (16) proposed an algorithm for the management of AML based on tumor size and symptoms. For small AML (≤ 4 cm), follow-up with ultrasound (US) imaging is recommended every 12 months; for small AML in symptomatic patients, arterial embolization or partial nephrectomy can be chosen although observation is often favored in clinical practice. Treatment is recommended for symptomatic patients with large tumors, especially if the AML has bled. In asymptomatic patients with large AML, follow-up with computed tomography (CT) or US is recommended (16). Other options introduced for AML treatment are transarterial ethanol and percutaneous ablation using cryoablation or radiofrequency (17–19).

In this article, we describe the radiological features of renal angiomyolipomatosis. A PubMed search was performed by a radiologist for the term “angiomyolipomatosis.” The research showed 20 articles published in a period from 1969 to 2013. A total of 10 articles were excluded: four in German, three in French, one in Russian, and two did not describe the radiological features of renal angiomyolipomatosis. The remaining 10 articles in English, Italian, and Spanish languages describing radiological features of renal angiomyolipomatosis were selected.

Angiomyolipomatosis in Tuberous Sclerosis Complex

Tuberous sclerosis is largely the result of loss-of-function mutations of TSC1 (9q34) or TSC2 (16p13.3) genes. In addition to conditions such as mental retardation and seizures, TSC is associated with AMLs, LAM, pulmonary multifocal micronodular hyperplasia, subependymal giant cell tumors, cutaneous angiofibromas, and cardiac rhabdomyomas (20). AMLs occur in 55–75% of patients with TS; AMLs in TS typically develop at a young age and are frequently multiple, almost always bilateral and larger in size, presenting as angiomyolipomatosis (Figure 1) (11, 21). Patients with TSC are more likely to show multiple, bilateral, and larger AMLs than AMLs in sporadic cases (22, 23). Most of the AMLs in TSC manifest as the classic type, while fat-poor AMLs are found in over one-third of these patients. Fat-poor AMLs in TSC tend to be larger than those of the sporadic form (24).

As renal cell carcinoma may occur in patients with TSC, renal masses without visible characteristic adipose tissue may require a percutaneous biopsy or closer follow-up (15). Patients with TSC have also shown the presence of epithelioid AML and AML with epithelial cysts; TSC patients are more likely to show these two variants of AML compared to AMLs found sporadically (25, 26). Epithelioid AML shows variable biological behavior including malignancy; in fact, during adulthood, it can infiltrate adjacent tissue or metastasize to the lungs, liver, peritoneum, or bone (27, 28).

As patients with TSC risk premature loss of nephrons due to increasing numbers and dimensions of cysts and AMLs, selective arterial embolization, percutaneous ablation, or partial nephrectomy are preferred conservative therapies for the treatment of these lesions (29). Moreover, these patients present a high risk of spontaneous hemorrhage; AML >4 cm and AML aneurysms >0.5 cm are risk factors for AML

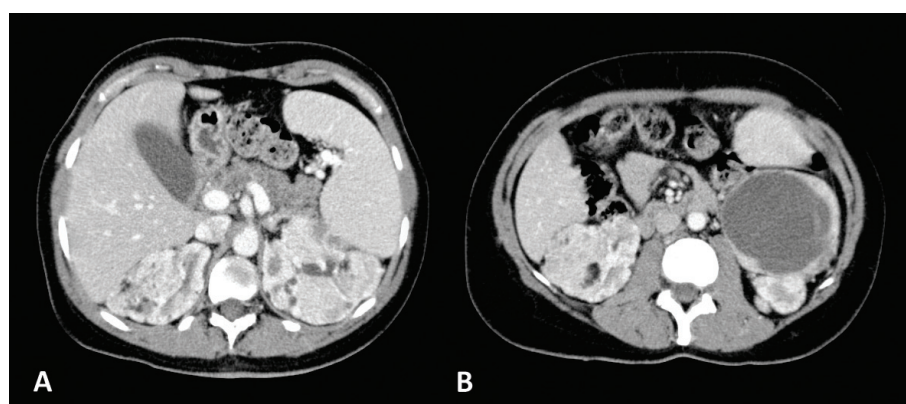


Figure 1. CT axial scan of the abdomen during venous phase of a 45-year-old woman with TS showing the presence of renal angiomyolipomatosis (A and B) and caliectasia at the level of the left upper calyceal group (A). Furthermore, a cystic lesion with solid peripheral tissue indissociable from the left inferior renal pole is evident (B). At the follow-up CT scan performed approximately 6 months later, the cystic lesion showed an increase of the solid component. Consequently, the patient underwent left nephrectomy and tumorectomy. Histological examination revealed the diagnosis of dedifferentiated liposarcoma.

hemorrhage (30, 31). Approximately 43% of patients with TSC may have recurrent AML bleeding, which is not usually seen in sporadic AMLs (32, 33). Indeed, angiomyolipomatosis is often associated with multiple spontaneous bleeding events. The mTOR inhibitor sirolimus allows the prevention of tumor growth and recurrence of bleeding in patients with TSC by inhibiting the activation of the mTOR pathway (34). Transcatheter embolization is an effective treatment for controlling bleeding in the acute context and can be performed in combination with surgery (17).

Angiomyolipomatosis in Lymphangioleiomyomatosis

Renal angiomyolipomatosis can be detected in patients with LAM, a rare disease characterized by destructive cystic changes in the lungs. Sporadic LAM manifests itself in one in 400,000 adult females; it may also happen in TSC, occurring in 30–40% of adult females and rarely in males and children (11, 35). In addition to renal AMLs, LAM presents other disorders including lymphangioleiomyomas,

abdominal lymphadenopathy, and chylous ascites, and an increase in the frequency of meningioma (11, 35–38). As well as sporadic AMLs, the guidelines for LAM patients with AMLs recommend US examination per year for small AMLs (<4 cm), while larger AMLs and AMLs with aneurysms of 5 mm or greater diameter should be checked twice a year with US examination. The treatments of choice for a bleeding AML are renal arterial embolization and partial nephrectomy. Furthermore, the mTOR inhibitor sirolimus reduces the volume of AML (34, 35, 39).

Imaging Features of Angiomyolipomatosis

Several studies have described the radiological features of angiomyolipomatosis; for this review, we analyzed the radiological features described in several clinical cases. Imaging features of the cases of renal angiomyolipomatosis described in the literature are listed in Table 1 (40–49).

Renal angiomyolipomatosis generally occurs with multiple and diffuse AMLs, bilaterally localized. Often the masses extend almost entirely covering the abdomen, displacing the

Table 1. Imaging features of cases of renal angiomyolipomatosis

References	Imaging method	Imaging features
Segal et al. (40)	Angiography	Hypervascular Renal enlargement Deformed calyces
Ahuja et al. (41)	Radiography	Thick mass of soft tissue with many thin cloud-like calcification figures
	Excretory urogram	Marked congestion and stenosis of the left ureteral outlet Left kidney well delimited Right calico-pielic cavities deformed Right kidney not well defined
	Angiography	Prominent vascular tortuosity with aneurysmal dilatation at lower pole of the left kidney Altered vascular architecture with peripheral ectasies and microaneurysm of the right kidney; furthermore, the lower pole showed a region with a roundish morphology, highly vascularized, surrounded by wide arteries and a number of blood pools Delayed passage time
Kalra et al. (42)	Ultrasound	Dimensional increase of the kidneys Multiple bilateral echogenic masses
	Contrast enhancement computed tomography	Numerous irregular hypodense areas of adipose tissue density Numerous isodense to hyperdense areas varying from soft tissue density to blood density Poor excretion of contrast medium

(Continued)

Table 1. (Continued)

References	Imaging method	Imaging features
Granata et al. (43)	Ultrasound and color-power-doppler (first patient)	Dimensional increase of the kidneys Hyperechogenic parenchyma No evidence of cortico-medullary differentiation Absence of localized hypervascularization areas Four renal cysts Hypoechoic area in the right upper pole
	Contrast enhancement magnetic resonance imaging (first patient)	Coarse localized mass at the right upper pole of difficult interpretation. The differential diagnosis was with fat-poor AML, epithelioid AML, and renal cell carcinoma; biopsy examination showed a diagnosis of fat-poor AML
	Ultrasound (second patient)	Dimensional increase of the kidneys Irregular profiles of the kidneys Structural subversion of the renal parenchyma with numerous and coarse nodules that alter to cysts
	Magnetic resonance imaging (second patient)	Numerous bilateral AMLs
Liu et al. (44)	Unenhanced computed tomography	Huge bilateral masses consisting primarily of adipose tissue
Ponce Díaz-Reixa et al. (45)	Ultrasound and contrast enhancement computed tomography (first patient)	Bilateral AMLs
	Ultrasound (second patient)	Nodule of the right kidney isoecogenous compared to perirenal adipose tissue
	Contrast enhancement computed tomography (second patient)	Mass at the right kidney, with heterogeneous appearance and adipose areas in the context, highly suggestive of AML Histological and immunohistochemical examination confirmed the diagnosis of AML
	Computed tomography (third patient)	Mass at the right kidney, compatible with AML Histological examination of the tumor demonstrated AML with epithelioid areas with infiltration of two lymph nodes that showed the same histological diagnosis
Er et al. (46)	Unenhanced computed tomography	Bilateral, renal masses (massive in the right kidney), with the density of adipose tissue
Incedayi et al. (47)	Ultrasound	Multiple bilateral hyperechogenic renal masses
	Unenhanced computed tomography	Massive renal masses Fluid accumulation and high-density areas at the right kidney, developed following the previous hemorrhage
Stallone et al. (48)	Ultrasound	Multiple renal hyperechogenic lesions
	Contrast enhancement computed tomography	Multiple renal lesions, describing a framework compatible with angiomyolipomatosis. Histological analysis confirmed the diagnosis of angiomyolipomatosis
Vernani et al. (49)	Unenhanced computed tomography	Widespread angiomyolipomatosis in the context of which fat components and soft-tissue tumor components were evident; hematomas were also present

AML, angiomyolipoma.

intestine. Signs of previous bleeding may be present. Renal cysts could also be detected. In AMLs with a predominantly fatty component, the adipose tissue localized within these lesions assumes fundamental importance in the diagnosis. On US examination, it appears hyperechoic compared to renal cortex. In CT examination, it appears as hypodense area of adipose tissue density, mixed, or with soft-tissue attenuation due to vascular or smooth muscle components, hemorrhage or fibrosis (2).

Bosniak described the angiographic features of AML. The author observed three patterns in particular: aneurysmal and tortuous vessels, berry-like aneurysms, and slow-flowing vessels with contrast medium retention (50).

On magnetic resonance imaging (MRI), it appears isointense compared with fat on T1-weighted images; moreover, with the use of in-phase and opposed-phase imaging, AMLs with predominant adipose component show the characteristic India ink artifact that appears at the interface between the lesion and the normal renal parenchyma on opposed-phase T1-weighted images. In T2-weighted images, however, the intensity can be variable, depending on the amount of adipose tissue present in the lesion, resulting homogeneously high in AMLs with a higher adipose component (Figure 2) (51–54).

The diagnosis is more difficult if there is the presence of fat-poor AML, epithelial AML, and AML with epithelial cysts, as we must discriminate these lesions from malignant lesions, such as renal cell carcinoma or the same epithelioid AML with malignant biological behavior, being able to be present in renal angiomyolipomatosis. For example, it is difficult to differentiate fat-poor AML from other solid tumors, especially renal cell carcinoma. In this case, double-echo gradient-echo chemical-shift MRI could be used in which the values of the signal intensity are measured on the renal lesion and on the spleen in on-phase and opposed-phase T1-weighted gradient-echo MRI (54). The presence of small calcifications within the lesion, which can be easily detected with CT, is considered to be suggestive of renal cell carcinoma (55). Furthermore, central necrosis is indicative of renal cell carcinoma, this being frequently present in medium-to-large clear cell renal cell carcinoma and very rare in AML. In fat-poor AML, the low amounts of adipose tissue can be detected on opposed-phase and in-phase imaging. It also appears homogeneously hypointense on T2-weighted images (53).

Finally, even contrast enhancement US can be used in the differential diagnosis between malignant and benign renal lesions (56). In a retrospective study, Lu et al. found a slow

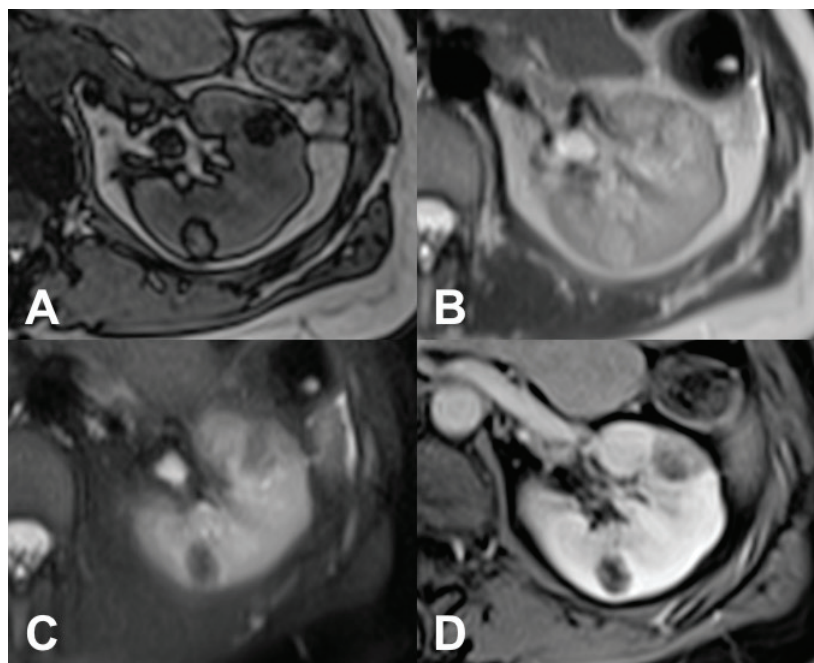


Figure 2. MRI axial scan of the abdomen shows two AMLs of the left kidney. (A) Opposed-phase shows the characteristic India ink artifact of the AMLs. (B) AMLs appear hyperintense on T2-weighted images and (C) hypointense on T2-weighted images with fat suppression. (D) T1-weighted image with fat suppression shows contrast enhancement of the AMLs.

centripetal enhancement in the cortical phase and a homogeneous enhancement in the peak phase in fat-poor renal AML (57).

Radiologic Diagnosis of Renal Angiomyolipoma

Jinzaki et al. proposed an AML classification in which clinical features, radiologic features, and pathologic features co-exist. This section focuses on the radiologic characteristics indicated in the AML classification of Jinzaki et al. (11).

Classic angiomyolipoma

Classic AML is a subtype of triphasic AML. The typical characteristic of classic AML is the presence of abundant adipose tissue (11). This AML almost always appears markedly hyperechoic compared to the renal parenchyma. In addition, 21–33% of AMLs smaller than 3 cm show acoustic shadowing (58, 59). The fat present in AML can be identified on unenhanced CT with a region of interest (ROI) showing an attenuation less than -10 HU (Figure 3) (50, 60, 61). The CT features of classic AML vary due to variable amounts of the three components present in the lesion (11). Furthermore, intralesional hemorrhage may be present, especially in

tumors larger than 4 cm (62). MRI can be used to diagnose AML also by detecting fat cells; India ink artifact visible with a loss of signal at the boundary between the mass and the renal parenchyma is indicative of AML (52).

Differential diagnosis of classic AML is with renal cell carcinoma, Wilms tumor, and retroperitoneal liposarcoma and teratoma (11).

Fat-poor angiomyolipoma

Fat-poor AMLs are those triphasic AMLs that contain too little fat to be identified with unenhanced CT (4, 63). There are three subtypes of fat-poor AML; their subdivision is based on the number of fat cells and their distribution within the lesion; they are hyperattenuating and isoattenuating AMLs, and AML with epithelial cysts (64).

Hyperattenuating angiomyolipoma

Hyperattenuating AML makes up about 4–5% of all AMLs (65). This subtype of fat-poor AML is generally small, with an average of 3 cm of diameter, and accounts for only 4% (3–10% range) of fat cells (65–67). As there is an abundant amount of smooth muscle component, they present characteristics similar to those of smooth muscle: they appear

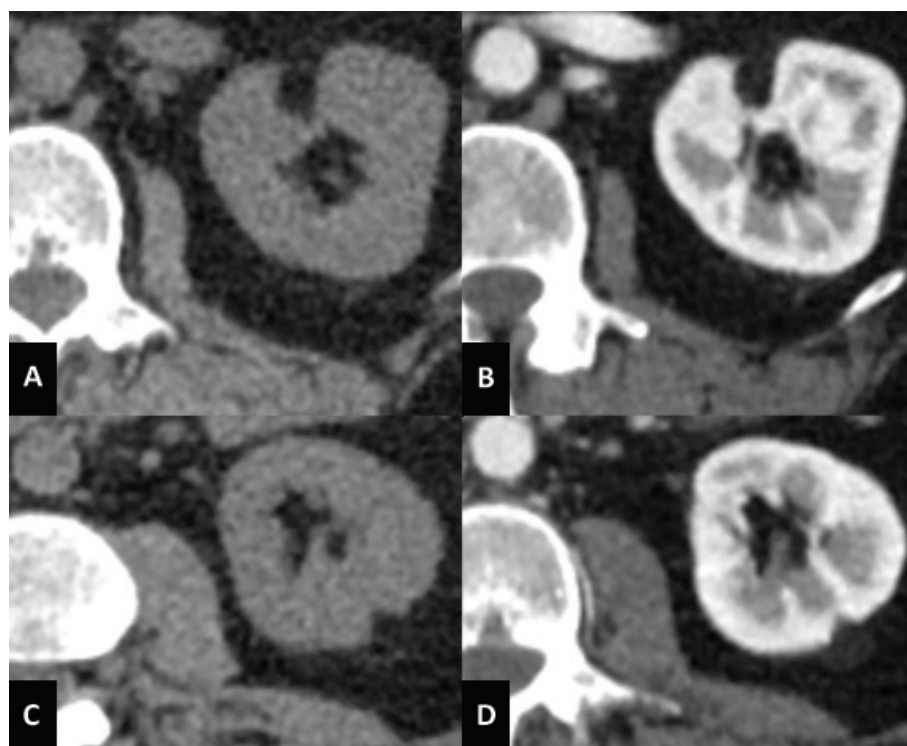


Figure 3. Unenhanced CT axial scan of the abdomen (A and C) and CT of the abdomen during arterial phase (B and D) of a 53-year-old woman showing the presence of classic AMLs, recognizable by the adipose component of the lesion.

hyperattenuating compared to renal parenchyma on unenhanced CT (usually greater than 45 HU); T1-hypointense and T2-hypointense on MRI; no signal loss on fat-suppressed pulse sequences, and chemical shift suppression; and isoechoic on US, with one study suggesting could be hyperechoic (65–67). Differential diagnosis of hyperattenuating AML is with renal cell carcinoma (typically the papillary renal cell carcinoma), metastases, oncocytoma, lymphoma, metanephric adenoma, and leiomyoma (63, 68).

Isoattenuating angiomyolipoma

Isoattenuating AMLs possess CT attenuations similar to those of the renal parenchyma on unenhanced CT. This type of AML does not possess regions of adipose tissue attenuation at unenhanced CT. In particular, fat cells are dispersed between smooth muscle and vessel components, too few to be detected with imaging but in sufficient quantities to reduce the overall attenuation compared to hyperattenuating AML (69). On MRI, this subtype of fat-poor AML appears typically T2-hypointense. This feature is given by its smooth muscle component (70). Furthermore, Jinzaki et al. claim that isoattenuating AML characteristics on all MRI pulse sequences are not well known because it is a rare lesion; this lesion may or may not show signal loss on fat-suppressed pulse sequences; the loss of signal depends both on the quantity and the distribution of fat cells within the lesion (11). It also shows chemical shift suppression (54, 70). Jinzaki et al. also state that, based on their experience, isoattenuating AML appears slightly hyperechoic on US (11). Differential diagnosis of isoattenuating AML is with renal cell carcinoma (11).

Angiomyolipoma with epithelial cysts

AML with epithelial cysts is a very rare variant of the fat-poor AML which contains epithelial-lined cysts. These AMLs have very few or no fat cells (71). This subtype of AML is benign and more common in female (69, 71–74). AML with epithelial cysts contains smooth muscle component, which represents the predominant component, and epithelial cysts and subepithelial stroma, which are typical of this subtype of fat-poor AML (69, 72). The imaging features of AML with epithelial cyst are not fully understood. A case was described in which the lesion presented a small cyst, and a non-cystic part that enhanced homogeneously. This lesion appeared hyperattenuating on unenhanced CT and, on MRI, T2-hypointense for the smooth muscle component (71). Another case described a multilocular cystic mass with the cystic component separated from that smooth muscle (73). Differential diagnosis is with multilocular cystic renal cell carcinoma, multilocular cyst, cystic nephroma, and a mixed epithelial and stromal tumor (73, 75).

Epithelioid angiomyolipoma

Epithelioid AML is a subtype of extremely rare potentially malignant AML (3, 25). Male and female are equally affected and the average age is 38 years (3). Approximately one-third has local extension or metastasis at diagnosis (76). Epithelioid AML contains numerous atypical epithelioid muscle cells; in most of these lesions there are few or no fat cells (25, 77, 78). This AML subtype typically appears as large masses (≥ 5 cm in size) with intralesional hemorrhage and necrosis; it can also be detected as spontaneous perirenal hematoma (79–85). These lesions may show small foci of adipose tissue on CT or MRI; moreover, epithelioid AML appears hyperattenuating on unenhanced CT (typically greater than 45 HU) and T2-hypointense (due to epithelioid muscle component) (83, 84). Furthermore, this AML subtype may appear as solid masses that enhance homogeneously or heterogeneously or as multilocular cystic masses (84). Differential diagnosis of epithelioid AML is with renal cell carcinoma and cystic renal cell carcinoma (25, 77, 84).

New Radiologic Classification of Renal Angiomyolipoma

Song et al. classified renal AML into fat-rich, fat-poor, and fat-invisible AML based on the amount of fat detected by CT or MRI (86). Fat-rich AML was identified by attenuation value less than or equal to -10 HU obtained by placing a ROI in the most hypodense area of the lesion (61). When the most hypodense area showed attenuation value greater than -10 HU, the chemical shift imaging was evaluated. Tumor-to-spleen ratio and signal intensity index were calculated using the values obtained by placing the ROI in the most hypointense area on opposed-phase images. Fat-poor AML was detected when the tumor-to-spleen ratio was <0.71 or when the signal intensity index value was $>16.5\%$. Fat-invisible AML was detected when the tumor-to-spleen ratio was ≥ 0.71 and when the signal intensity index value was $\leq 16.5\%$ (86). Both fat-poor AML and fat-invisible AML exhibit attenuation values greater than -10 HU on unenhanced CT. Song et al. showed that the attenuation value of fat-invisible AML detected in the ROI located in the most hypodense area of the lesion was greater than that of the fat-poor AML (86).

Conclusion

Renal angiomyolipomatosis is a common manifestation in patients with TS and LAM. AMLs are larger, multiple, almost always bilateral, and have a greater predisposition to bleeding, which is the reason why follow-up must be performed in these patients. Furthermore, specific subtypes of AML, such as poor-fat AML, are difficult to distinguish from malignant lesions. For this reason, further imaging examinations must be performed to obtain further information on the nature of the lesions.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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